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# United States Patent [19]

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Bergamini et al.

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[54] **DICLOFENAC AND TOBRAMYCIN FORMULATIONS FOR OPHTHALMIC AND OTIC TOPICAL USE**

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[51] Int. Cl.<sup>6</sup> ..... **A61K 31/74**

[52] U.S. Cl. .... **424/78.04; 424/78.05; 514/912; 514/914**

[58] Field of Search ..... **424/78.04, 78.05; 514/912, 914**

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

4,087,538	5/1978	Portnoff	.....	514/420
4,407,792	10/1983	Schoenwald et al.	.....	514/397
4,478,822	10/1984	Hasam et al.	.....	424/94.6
4,668,506	5/1987	Bawa	.....	424/429
4,829,088	5/1989	Doulakas	.....	514/567

**FOREIGN PATENT DOCUMENTS**

2013188	9/1990	Canada	.
0038698A2	10/1981	European Pat. Off.	.
0306984A1	3/1989	European Pat. Off.	.
WO89/09057	10/1989	WIPO	.

**OTHER PUBLICATIONS**

*Human Conjunctivitis*, Howard M. Leibowitz, MD, et al., Arch Ophthalmol, vol. 94, Oct. 1976, pp. 1752-1756.

*Association diclofenac-dexamethasone dans le traitement de l'inflammation postopératoire: étude prospective en double-insu*, Dr. Philippe Othenin-Girard, et al., Klin. Mbl. Augenheilk, 200, 1992, pp. 362-366.

*The Effect of 0.1% Indomethacin Eyedrops on Cataract Surgery*, Journal of Ocular Pharmacology, vol. 7, No. 1, 1991, pp. 77-81.

*The Effect of Ketorolac Tromethamine in Reducing Postoperative Inflammation: Double-Mask Parallel Comparison with Dexamethasone*, Allan J. Flach, MD, et al., Ann Ophthalmol 1989; 21:407-411.

*Infections of the Eye—35. Endophthalmitis*, David W. Parke II, et al., pp. 563-583.

*Incompatibility of indometacin and benzalkonium in eye drops due to ion-pair formation*, S. M. Dreijer-Van Der Glas, et al., vol. 9, 1987, Pharmaceutisch Weekblad Scientific Edition, pp. 29-32.

*Effects of Pretreatment with Mydriatics on Intraocular Penetration of 0.1% Pranopfen*, Takahiro Ogawa, et al., Jpn J Ophthalmol, vol. 37: 47-55, 1993.

*Prediction of Skin Permeability of Drugs: Comparison of Human and Hairless Rat Skin*, Yasunori Morimoto, et al., J. Pharm. Pharmacol. 1992, 44: 634-639.

*Binary Diclogenic Diethylamine-Water Systems: Micelles, Vesicles and Lyotropic Liquid Crystals*, Katrin Kriwet, et al., Eur. J. Pharm. Biopharm, 39 (6) 234-238, 1993.

*Degradation of Tobramycin in Aqueous Solution*, Michael Brandl and Leo Gu, Drug Development and Industrial Pharmacy, 18(13), 1423-1436, 1992.

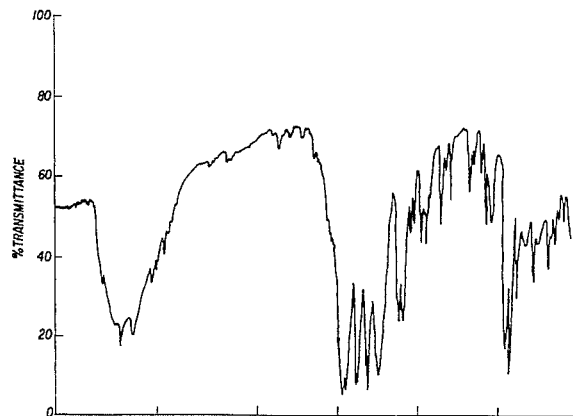
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[57] **ABSTRACT**

This invention includes a pharmaceutically acceptable formulation of Diclofenac, Tobramycin, a solubility agent and, optionally, excipients, tonicifiers, buffers, viscosity modifying agents, preservatives, and chelating agents, at a pH from greater than 7.0 to about 9. The invention also discloses the use of this pharmaceutically acceptable formulation of an antibiotic and NSAIDs to treat eye and ear conditions accompanied by infection and inflammation.

**96 Claims, 4 Drawing Sheets**



## OTHER PUBLICATIONS

*Spectrophotometric Method for Determination of Tobramycin, Apramycin and Kanamycin in Formulations*, P. R. Bontchev, et al., *Mikrochimica Acta (wien)* 1984 III, 459–465.

*The Top Ten NSAIDs – A molecular modelling study*, S. Winiwarter, et al., *Pharmaceutica Acta Helvetiae* 68 (1994) 181–189.

*Conjunctival Disorders*, *Current Veterinary Therapy X Small Animal Practice*, Cecil P. Moore, D.V.M., 1989, pp. 673–678.

*A New Corticosteroid–Antibiotic Preparation in Eye and Ear Infections*, *General Practitioner Clinical Trials*, Alexander, J. et al., Jul., 1966, vol. 197: 94–96.

*Canine Conjunctiva and Nictitating Membrane*, *Veterinary Ophthalmology*, Dennis E. Brooke, pp. 290–304, 1991.

*Diseases of the Ear*, *Textbook of Veterinary Internal Medicine — Diseases of the Dog and Cat*, vol. I, Dennis W. Macy, pp. 246–257.

American Academy of Ophthalmology, Final Program, Scientific Posters, p. 101.

XXVIIth International Congress of Ophthalmology '94, Final Program, Scientific Papers.

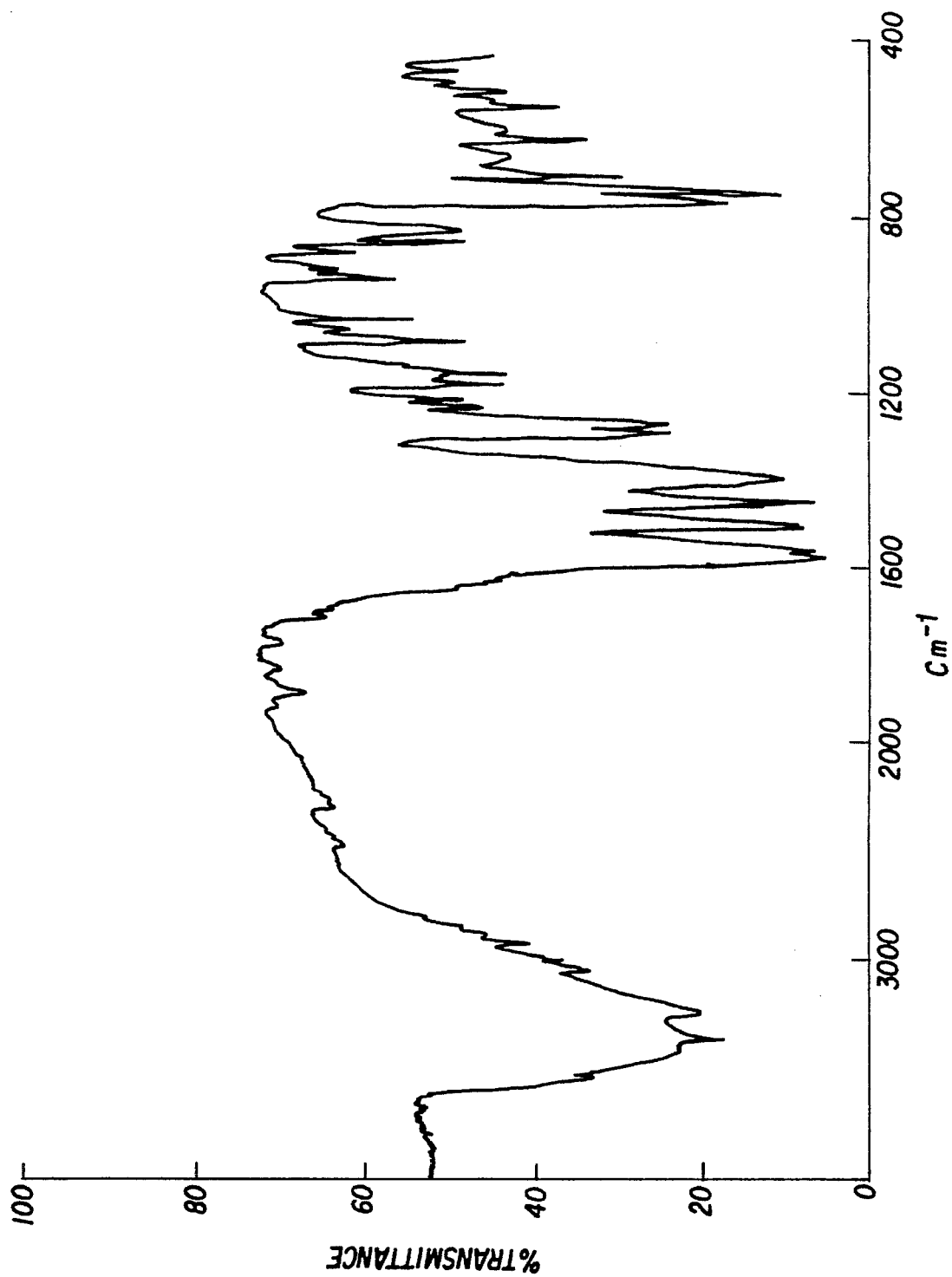
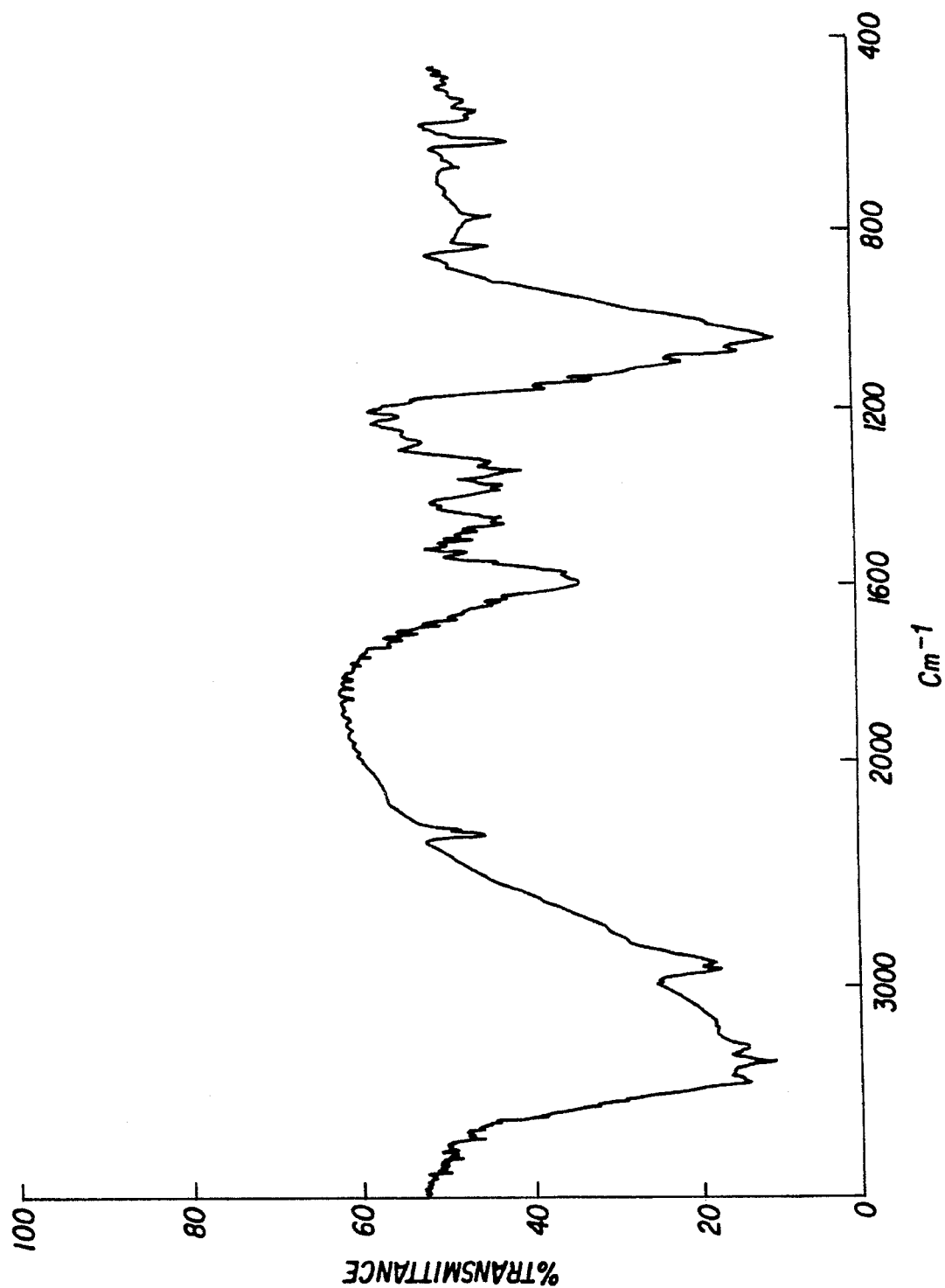
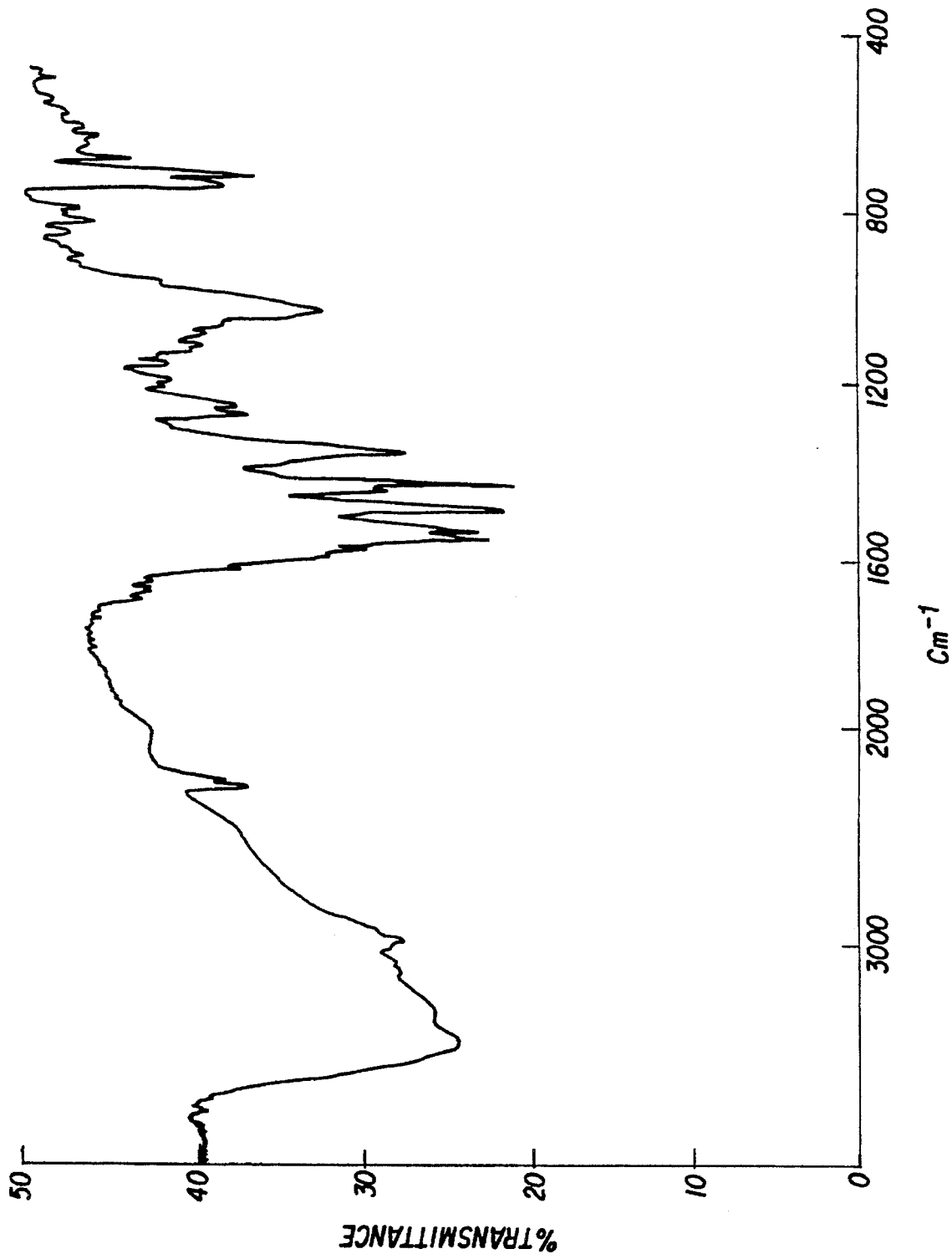


FIG. 1(a)



**FIG. 1(b)**



**FIG. 1(c)**

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